DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Victor Raczkowski, M.D.
Vice President, U.S. Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062

APR 25 2008

Re: Docket No. FDA-2007-P-0169

Dear Dr. Raczkowski:

This responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Unimed Pharmaceuticals, Inc. (Unimed), a subsidiary of Solvay Pharmaceuticals, Inc., on October 29, 2007 (Petition).[1] The petition requests that we require any abbreviated new drug application (ANDA) for a generic version of Marinol to contain, not only the indication and safety information for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, but also the indication and safety information for the treatment of anorexia associated with weight loss in patients with AIDS.

We have carefully reviewed the arguments in your petition, the comments in opposition to your petition submitted by Rakoczy Molino Mazzochi Siwik LLP on behalf of Cobalt Laboratories Inc., dated January 22, 2008, and your comments in response dated April 3, 2008. For the reasons stated below, we deny your request. In accordance with the Federal Food, Drug, and Cosmetic Act (the Act), FDA regulations, and case law, the Agency may approve an ANDA for a dronabinol product whose labeling omits information relating to use of the drug to treat anorexia associated with weight loss in AIDS patients.

I. BACKGROUND

A. Marinol

Dronabinol is a cannabinoid that affects the central nervous system and is a stimulant of central sympathomimetic activity. The drug is abusable and is a Schedule III controlled substance under the Controlled Substances Act (21 U.S.C. 812(b)(3)) and 21 CFR 1308.13(g).

[1] This citizen petition was originally assigned docket number 2007P-0418/CP1. The number was changed to FDA-2007-P-0169 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

On May 31, 1985, FDA approved the new drug application (NDA 18-651) for Unimed's dronabinol product, Marinol, for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments (the CINV indication). Marinol is marketed as 2.5 milligram (mg), 5 mg, and 10 mg capsules. The 7 years of orphan drug exclusivity for this indication under section 527(a) of the Act (21 U.S.C. 360cc(a)) has expired. On December 22, 1992, we approved Marinol for the treatment of anorexia associated with weight loss in patients with AIDS (the AIDS indication). The AIDS indication for Marinol is protected by U.S. Patent No. 6,703,418 (the '418 patent), which expires on February 26, 2011.

B. Patent Protection for NDAs and Labeling Differences for ANDAs

Before addressing the arguments you make in your petition, it is appropriate to summarize the statutory and regulatory provisions relevant to the approval of a generic drug product whose labeling omits an indication that is protected by a patent.

The Act and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance, drug product, or approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[2] FDA is required to publish patent information for drugs approved under section 505(c), and does so in its *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book" (sections 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) is known as a *listed drug*.[3] Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort

[2] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[3] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (§ 314.53(e)).

needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, and route of administration), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[4] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, for each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed (Paragraph I certification);
(II) that such patent has expired (Paragraph II certification);
(III) that the patent will expire on a particular date (Paragraph III certification);
(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought (Paragraph IV certification).

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be

[4] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Because Unimed's orphan drug marketing exclusivity for Marinol has expired and Unimed currently has no other marketing exclusivity for dronabinol, this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

These four certifications are not the only manner in which an ANDA applicant may address all relevant patents. An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph I-IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method of use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[5]

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states that:

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[5] The Agency's interpretation of the plain language of the Act is further supported by Congressional intent as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[6]

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[7]

The right to file a section viii statement and carve out from labeling method of use information protected by a patent has been upheld by the courts. In *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent and, under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all listed patents have (1) expired, (2) been successfully challenged, (3) been subject to a paragraph IV certification pursuant to which the patent

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[6] FDA regulations implementing this statutory provision use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[7] See also the final rule entitled *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed*, 68 FR 36676 (June 18, 2003). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "Our position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

owner or NDA holder has declined to sue within 45 days, (4) been subject to a paragraph IV certification that led to a lawsuit and a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

C. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress' intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. In § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[8]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA

[8] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

> labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(4)(D) of the Act.[9]

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use."

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb* v. *Shalala*, F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc.* v. *Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer.

Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally permitted as a permissible difference due to difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. ANALYSIS

You state that you have reason to believe that there are one or more pending ANDAs seeking approval of a generic version of Marinol without the AIDS indication. You state that if approved, such a product would have neither the prescribing information (in the package insert) nor the patient information leaflet created especially for Marinol's AIDS indication. You claim that, without this labeling, a generic product: (1) would be misbranded under section 502(a) of the Act (21 U.S.C. 352(a)) because the labeling would not provide material information necessary for a "customary or usual" use of the generic drug (i.e., the AIDS indication), which would make the labeling misleading under section 201(n) of the Act (21 U.S.C. 321(n)); and (2) would be unable to adequately promote the safe and effective use of dronabinol in AIDS patients (Petition at 2).

For the reasons stated below, we are denying your petition. A generic version of Marinol would not be misbranded because it lacked the AIDS indication, and there is no basis for requiring that such a product promote the safe and effective use of dronabinol in AIDS patients when the ANDA applicant does not seek approval for the AIDS indication.

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[9] We note that, because of a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

In our April 6, 2004, response to the citizen petition in Docket No. 2003P-0321/CP1,[10] we affirmed our authority to approve generic ribavirin drug products with labeling that omits protected information, and rejected arguments similar to the ones you are making here. We reiterated this position in our March 13, 2008, response to a citizen petition in Docket No. 2006P-0410/CP1 concerning ANDAs for amifostine with a protected indication carved out.[11] In rejecting your arguments as discussed below, we again reaffirm our authority to approve generic drug products with carved-out labeling, and we deny your request that any ANDA for a generic version of Marinol be required to include the AIDS indication, as this would mean that we could not approve such an ANDA until the patent covering the AIDS indication had expired, been successfully challenged, or otherwise ceased to be a barrier to approval (e.g., after expiration of the 30-month stay).

A. Labeling for a Generic Version of Marinol With the AIDS Indication Carved Out Will Not Be Misleading Under the Act and FDA Regulations.

You state that you do not challenge our general authority to permit ANDA applicants to carve out protected indications or other protected conditions of use under the Act and §§ 314.94(a)(8)(iv) and 314.127(a)(7). Moreover, you acknowledge, as you must, that our authority to do so has been upheld by the courts. You also acknowledge that we do not regulate the substitution of generic drug products for innovator drug products. Nevertheless, you maintain that with regard to Marinol in particular, we should require that a generic version contain the carved-out AIDS indication because without that indication the product and patient labeling would be misleading, in violation of sections 502(a)[12] and 201(n)[13] of the Act (Petition at 4 to 5).

You state that our authority to approve a generic drug product with carved-out labeling must be read in conjunction with sections 502(a) and 201(n). You state that under section 201(n), if a product's labeling fails to reveal material facts concerning the consequences that may result from use of the product under customary or usual conditions of use, the labeling is misleading and the product is misbranded. You contend that because of the

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[10] April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1 (Ribavirin Response Letter).

[11] March 13, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., Docket No. 2006P-0410/CP1 (Amifostine Response Letter).

[12] Under section 502(a), a drug is misbranded, in pertinent part, if its labeling is false or misleading in any particular.

[13] Under section 201(n), if an article is alleged to be misbranded because the labeling or advertising is misleading, in determining whether labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

substantially different daily dose, timing of administration, duration of treatment, and likelihood of central nervous system adverse events for the AIDS indication, dronabinol labeling with information concerning the AIDS indication carved out would fail to reveal material facts about the consequences resulting from use of the drug for that unapproved indication. You contend that for purposes of sections 502(a) and 201(n), the most customary or usual use of a generic version of Marinol will be as an appetite stimulant for AIDS patients (Petition at 5 to 7).[14]

You do not provide adequate support for your contention that the circumstances regarding the use of Marinol justify rejecting FDA's acknowledged authority to approve generic drugs with carved-out indications. As we explained in our response to a similar argument in the Amifostine Response Letter, your interpretation of the misbranding provisions in sections 502(a) and 201(n) of the Act cannot be reconciled with a reading of the Act as a whole. If a carve-out of protected information that did not render a drug less safe and effective for the remaining nonprotected conditions of use would nonetheless render the drug misbranded for failure to include information pertinent to the carved-out use, the provisions permitting such carve-outs would be superfluous. To interpret these provisions as you do would be to read section 505(j)(2)(A)(viii) (permitting the ANDA applicant to decline to seek approval for one or more patented conditions of use) out of the statute. Such a reading would be contrary to the fundamental canon that an individual statutory provision should be construed in the context of the statutory scheme in which it appears.[15] As stated in section I.B of this response, in authorizing the submission of a section viii statement, the Act allows an ANDA applicant to carve out from labeling a method of use claimed by a listed patent.

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[14] You contend that your interpretation of customary or usual use in section 201(n) of the Act is supported by statements in our rulemaking to require drug sponsors of drugs that have indications occurring both in adults and children to conduct pediatric clinical studies of those drugs in those indications under certain circumstances. You note that in the preamble to the proposed rule, the Agency stated that we may consider pediatric use to be "customary or usual" when the drug is indicated for a disease or condition that affects both children and adults and is not contraindicated in children (citing 62 FR 43000 at 43907-43908 (August 15, 1997)). You further state that in the preamble to the final rule, we maintained that the uses for which a drug must be adequately labeled go beyond those explicitly included in product labeling (citing 63 FR 66632 at 66657-66658 (December 2, 1998)). You state that having articulated this position, we "cannot disavow it without a clear explanation of the policy basis for doing so" (Petition at 7). As you note, however, the 1998 final rule on pediatric studies was invalidated by the court in *Ass'n of American Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002), on the ground that FDA overstepped its bounds in promulgating it without more explicit statutory authority to do so. In addition, even had that rule been upheld, as explained in greater detail below, references to previous Agency statements about the meaning of "customary or usual use" under section 201(n) in contexts other than generic labeling carve-outs are inapposite to the question of whether a generic version of Marinol with the AIDS indication omitted is misbranded, because the Act and FDA regulations specifically authorize us to approve generic drugs with patent-protected indications omitted as long as the drugs are safe and effective for the remaining nonprotected conditions of use.

[15] *See United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988); *Gustafson v. Alloyd Co.*, 513 U.S. 561, 568 (1995).

Although the Act requires that an ANDA contain information showing that the proposed conditions of use have been previously approved for the listed drug, the Act does not require that an ANDA be approved for each indication for which the reference listed drug is approved. Similarly, although the Act requires that the labeling of a generic drug be the same as the labeling approved for the listed drug, it provides an exception for changes resulting from the fact that the generic drug and the listed drug are produced or distributed by different manufacturers.

Your position — that the labeling for a generic dronabinol product without the AIDS indication is misleading under sections 502(a) and 201(n) of the Act because the drug will be prescribed off label for the AIDS indication — would effectively nullify the provisions in the Act that permit the approval of a generic drug with a carved-out indication. Conversely, our interpretation — that a generic drug product is not misbranded if its labeling omits an indication protected by patent — is consistent with the Act's provisions on ANDA patent certifications and sameness of conditions of use and labeling for generic products, yet still gives effect to statutory provisions regarding misbranding and adequate directions for use (in circumstances where the law does not specifically permit omission of protected information).

Moreover, unlike your interpretation of the misbranding provisions, our interpretation is consistent with the underlying goals of the Hatch-Waxman Amendments. The Hatch-Waxman Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing provisions that protect certain aspects of innovator drugs from generic competition for certain periods of time. As a quid pro quo for this increased protection, the Amendments created an abbreviated approval mechanism allowing sponsors of generic drugs to rely on the Agency's findings of safety and effectiveness for innovator drugs in seeking approval of their generic drug products when intellectual property barriers to approval expire or are otherwise removed.

The Amendments thus strike a balance between encouraging the research and development of new drugs and enabling the marketing of lower-cost, generic versions of those drugs at the earliest possible time. Under your interpretation of the misbranding provisions, the existence of patent protection for Marinol's AIDS indication would prohibit the approval of a generic dronabinol product for any indication for the duration of the patent on the use of the drug for the AIDS indication, thereby completely eliminating the opportunity for consumers to benefit from the existence of a lower-cost generic product, even for the nonprotected CINV indication, during this period. On the other hand, our interpretation allows innovators to enjoy the benefits associated with their efforts to develop new indications (including patent protection and exclusivity for those indications) while promoting competition with respect to indications for which innovators are not entitled to protection (either because they have not conducted research that entitles them to protection or because any applicable protection has expired, been successfully challenged, or has otherwise ceased to be a barrier to approval).

B. Labeling for a Generic Version of Marinol Need Not Contain the AIDS Indication and Related Safety Information to Ensure the Safe and Effective Use of the Product.

You acknowledge that under § 314.127(a)(7), we may approve an ANDA containing proposed labeling that omits protected aspects of the listed drug's labeling if those omissions "do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use." However, you maintain that the intended reach of this regulation is broader than the text would suggest. In support of this, you cite the following statement in the preamble of the 1992 final rule on ANDA regulations that adopted § 314.127(a)(7): "FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy" (57 FR 17950 at 17968 (April 28, 1992)). You contend that if a generic dronabinol product that lacked the prescribing information and patient leaflet for the AIDS indication were used as an appetite stimulant in AIDS patients, this would pose a risk of medication errors due to improper dosage and usage (as the daily dose, timing of administration, and duration of treatment for the AIDS indication differ from those for the CINV indication). Therefore, you claim that approval of a generic dronabinol product with carved-out labeling would be contrary to our intended interpretation of § 314.127(a)(7) (Petition at 9 to 10).

Your argument misinterprets our statements in the 1992 ANDA final rule concerning § 314.127(a)(7). The quoted statement was in response to a comment stating that the regulation should reflect that labeling differences in a generic product might be due to patent protection (in addition to differences due to production or distribution by different manufacturers). We agreed with the comment regarding the need to revise the regulation so that it also covered labeling differences due to patents or exclusivity. The quoted statement in the final rule only summarizes the revised provision, which specifically authorizes the Agency to approve generic product labeling that omits protected portions of the innovator labeling when "such differences do not render the proposed drug product less safe or effective than the listed drug *for all remaining, nonprotected conditions of use*." Thus, the regulation requires us to look at whether the generic drug product that carves out patent- or exclusivity-protected labeling will remain safe and effective for its labeled indications (i.e., its remaining nonprotected conditions of use). It does not require us to consider the safety or effectiveness of that product for indications for which it will not be labeled. To interpret the statement you quote in the manner you suggest would effectively nullify an important aspect of the provision adopted in the final rule.

You state that the recommended starting dosage for the CINV indication is 5 mg/meter^2, or 5 mg, given 1 to 3 hours before chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of four to six times a day (with upward titration; most patients respond to 5 mg three or four times daily). In contrast, the recommended starting dosing for the AIDS indication is 2.5 mg twice daily, before lunch and dinner, with titration to a maximum of 10 mg twice a day or a minimum of 2.5 mg once a day, based on tolerability of side effects (Petition at 10 to 11).

You state that explicit dosing instructions for physicians and safety information for patients are needed for the two Marinol indications to prevent inappropriate medication use and patient harm due to adverse events. You note that Unimed provides a patient information leaflet to promote the safe and effective use of Marinol as an appetite stimulant by AIDS patients. You state that the patient leaflet is of critical importance for use in the AIDS indication because it consists of both drug-specific information and non-drug information relevant to AIDS patients that ensures the safety and efficacy of Marinol. You argue that the leaflet is especially important because it provides information on the adverse events associated with the AIDS indication, which are of greater significance for these patients (compared to CINV patients) because of the long duration of treatment for the AIDS indication. You state that the patient leaflet plays a significant role in promoting the safe and effective use of Marinol and is one reason we approved the material. You add that you distribute 2.5 mg Marinol, a strength intended primarily for AIDS patients, in unit-of-use packaging with the leaflet enclosed. You state that a generic version of Marinol approved solely for the CINV indication would not include the leaflet information provided to a patient prescribed Marinol for the AIDS indication; instead, the information provided to the patient who received the generic product would describe a dosing regimen that is two to sixteen times higher and two to six times more frequent than would be appropriate for an AIDS patient (Petition at 11 to 15).

As you acknowledge, the Act and FDA regulations give the Agency the authority to approve a generic drug product whose labeling carves out an indication of the reference listed drug, and the courts have recognized this authority. Given that fact, the relevant question with respect to the carve-out of the AIDS indication is whether the omission would render a generic dronabinol product less safe or effective than Marinol for the nonprotected, CINV indication under § 314.127(a)(7). You make no claim and provide no evidence that the carved-out labeling would make a generic dronabinol product less safe or effective in the treatment of cancer patients.[16] Although we agree that the recommended initial dosing for the AIDS indication is 2.5 mg twice daily, and the 2.5 mg dose is distributed in unit-of-use packaging, a patient undergoing chemotherapy might also be prescribed the same dose dispensed in the same packaging. Moreover, the lack of a patient information leaflet would not make a generic dronabinol product less safe for CINV patients. As you acknowledge, the leaflet was created at Unimed's initiative; we did not require the company to develop the leaflet to ensure the safe use of Marinol. In addition, the leaflet concerns only the AIDS indication, and therefore is unrelated to the safe and effective use of the drug for the CINV indication.

After reviewing the information available to us, we have concluded that a dronabinol product with the AIDS indication omitted would not be less safe or effective than

[16] The claims you make about the safety of a dronabinol product with the AIDS indication carved out only concern the use of such a product for the AIDS indication, not for the nonprotected CINV indication. As such, they are not relevant to the inquiry that the statute and regulations require.

Marinol for the CINV indication.[17] The generic labeling will include all of the information necessary to use dronabinol safely and effectively for the CINV indication (just as the Marinol labeling did before the AIDS indication was approved). Thus, the fact that the labeling for a proposed generic dronabinol product would omit information on Marinol's AIDS indication provides no basis for refusing to approve the ANDA for the CINV indication under the Act or our regulations.

Our approval of an ANDA for dronabinol with the AIDS indication omitted also would be consistent with our approvals of other generic drug products with carved-out indications and conditions of use. For example, in *Bristol-Myers Squibb*, the innovator company marketed the reference listed drug Capoten (captopril), which was approved and labeled with four indications. The ANDA applicant submitted an ANDA for a generic captopril drug product and referenced Capoten as the listed drug. We approved the ANDA with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication. The D.C. Circuit held that omission of the indications protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act (91 F.3d at 1500). Other examples of generic drug products with protected labeling carved out include:

- Tramadol with labeling that omitted a protected slower titration schedule but included information on the unprotected faster titration schedule also appearing in the labeling of the innovator product

- Oxandrolone with labeling that omitted protected information on geriatric use

- Ribavirin with labeling that omitted use of the drug in combination with PEG Intron (peginterferon alfa-2b) for a protected indication (see Ribavirin Response Letter)

- Amifostine with labeling that omitted a patent-protected indication (see Amifostine Response Letter)

Significantly, for three of these drugs (captopril, tramadol, amifostine), the carved-out indication had a lower dosing schedule than the nonprotected indication, as would be the case with a generic version of Marinol. Thus, in accord with FDA's statute, regulations, and long-standing Agency practice, the possibility that a generic dronabinol product

[17] This determination, based on our experience and expertise in reviewing product labeling and making judgments regarding the safety and effectiveness of drugs, is entitled to judicial deference (*Zeneca v. Shalala*, 213 F.3d 161, 169 (4th Cir. 2000)).

approved for the CINV indication might be prescribed by physicians to treat anorexia associated with weight loss in AIDS patients provides no basis for denying approval of an ANDA for dronabinol with the AIDS indication carved out. Requiring FDA to consider the safety and efficacy of a generic dronabinol product in the treatment of AIDS patients when the generic applicant does not seek approval for that indication would effectively create new approval requirements beyond those established by Congress and the Agency. In addition, it would be inconsistent with our long-standing policy of not interfering with the practice of medicine, in particular with physicians' ability to prescribe approved drug products for their patients for any purpose deemed appropriate in their professional judgment.

C. The Possibility That a Generic Version of Marinol Without the AIDS Indication Will Be Dispensed for That Indication Does Not Bar Approval of Such a Product.

You state that the pharmacy laws and regulations of all states allow a pharmacist to dispense a generic drug in place of a brand-name product named on a prescription, and in some states generic substitution is required absent express direction from the physician or patient. You also state that many state Medicaid programs and most private insurance programs have provisions that strongly encourage generic substitution. You further state that generic substitution policies are often based on FDA's Orange Book and apply to generic products that are listed in the Orange Book as "therapeutically equivalent" to brand-name products. You argue that an approved generic version of Marinol with the AIDS indication carved out will nevertheless be rated therapeutically equivalent to Marinol. You maintain that there will be no way for a pharmacist relying on the Orange Book to know that such a generic dronabinol product is not labeled for the AIDS indication. You contend that this will result in frequent dispensing of the generic product for the AIDS indication, even though the generic product does not contain patient information for that indication (Petition at 15 to 16).

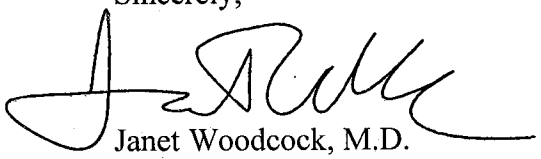
The existence of state generic drug substitution laws, which might require the substitution of a generic dronabinol product for Marinol, provides no basis for refusing to approve an ANDA for dronabinol without the AIDS indication. We acknowledge that in some states a generic dronabinol product might be substituted for Marinol even when the drug is intended for treating anorexia in AIDS patients, but we have no control over the operation of these substitution laws. As you note, in *Bristol-Myers Squibb*, the D.C. Circuit recognized that the existence of "some state laws and health insurers that mandate substitution of generic drugs" could diminish the value of marketing protection given to the manufacturers of innovator drugs under the Act (91 F.3d at 1500). However, you fail to mention that the court, although acknowledging the effect of this substitution, upheld FDA's interpretation of the Act and implementing regulations (e.g., §§ 314.94(a)(8)(iv) and 314.127(a)(7)) as permitting the Agency to approve an ANDA for a generic drug with labeling that omitted exclusivity-protected indications (and corresponding indication-specific dosing information) for which the innovator drug was approved. The court stated that the potential diminution in marketing protection was "not a sufficient basis upon which to conclude that the Congress intended to confer upon the

manufacturers of pioneer drugs the much broader protection" which would be conferred if we could not approve generic drug products with carved-out indications (id.). Thus, the fact that state substitution laws may result in the dispensing of generic dronabinol for the protected AIDS indication provides no basis for denying approval of an ANDA for a generic version of Marinol with the AIDS indication carved out.

III. CONCLUSION

We have reviewed your petition, the submitted comments, and other relevant information available to us. For the reasons stated above, we deny your request that we require any ANDA for a generic version of Marinol to contain the protected AIDS indication and safety information related to this indication. Instead, we have concluded that approval of a generic version of Marinol with the AIDS indication carved out would be consistent with the Act and FDA regulations because such a generic dronabinol product would be no less safe or effective for the remaining nonprotected condition of use (the CINV indication).

Sincerely,



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Director
Center for Drug Evaluation and Research